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TAKAHASHI KOICHI****(54) RESOLVENT COMPOSITION FOR SPARINGLY SOLUBLE MEDICINE****(57)Abstract:**

PURPOSE: To obtain the subject composition, composed of a polyhydric alcohol ester of a medium-chain fatty acid, excellent in percutaneous absorbability, stability, solubility and simplicity without any irritation and useful for an antipyretic, antiinflammatory and analgesic agent such as mefenamic acid.

CONSTITUTION: The objective composition is composed of (A) a polyhydric alcohol ester of a medium-chain fatty acid which is an ester of glycerol, ethylene glycol, propylene glycol or polyglycerol with a 6-12C fatty acid, preferably (A) the ester and (B) water. Furthermore, the blending ratio (A/B) of the ingredients (A) with (B) is preferably (50/50) to (90/10).

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(54)【発明の名称】 難溶解性薬物溶解剤組成物

(57)【要約】

【構成】多価アルコール中鎖脂肪酸エステルから成る難溶解性薬物溶解剤組成物。(第1発明)

乳酸アルキルエステル、二塩基酸アルキルエステル、多価アルコールアルキルエーテル、アシル化アミノ酸、脂肪アルコール、脂肪酸のうちの少なくとも1種から成る極性を有する油分から成る難溶解性薬物溶解剤組成物。

(第2発明)

【効果】第1発明及び第2発明の溶解剤組成物は、解熱消炎鎮痛薬が良好に溶解する。第1発明又は第2発明の溶解剤組成物に解熱消炎鎮痛薬が溶解して成る解熱消炎鎮痛剤組成物は、経皮吸収性に極めて優れ、刺激性がなく、製剤としての安定性、生体に対する安全性及び製造の簡便性に優れている。

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Translation of the relevant part of D3

RESOLVENT COMPOSITION FOR SPARINGLY SOLUBLE MEDICINE

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Problems to be Solved by the Invention

In general, the degree of drug absorption is enhanced when the drug is dissolved in oil rather than being dispersed.

However, many of the analgesic and antiphlogistic agents are highly crystalline and are thus poorly soluble. Therefore, crystals precipitate and grow over time, and the drug is not absorbed adequately in vivo, thereby making the drug unsatisfactory as a formulation in terms of the efficacy and effects thereof.

Although there is also a method for preparing an emulsion using oil, such as medium-chain fatty acid esters of glycerin or propylene glycol and lower alkyl esters of adipic acid or sebacic acid, these oil hardly emulsify and the emulsification stability is poor, thereby making it difficult to maintain long-term storage stability.

When enhancing the absorption by adding the aforementioned absorbefacient or ethanol etc., there are many problems in terms of side effects caused by these additives such as irritation.

Although it is further possible to enhance drug absorption by pulverizing and dispersing the drug in an emulsifying base, a problem remains in growth of drug crystals.

As described above, without the use of an irritating solvent, surfactant, or absorbefacient etc., it has been difficult to prepare a formulation in which drugs are stably dissolved for a long time without being precipitated and also exhibiting excellent absorption properties.

An object of the present invention is to provide a poorly-soluble drug solubilizing composition which solves the above-mentioned problems associated with conventional techniques.

Means for Solving the Problems

By taking the above problems into consideration, the present inventors studied intensively and extensively in order to develop an antipyretic, analgesic and antiphlogistic agent composition which is excellent in terms of absorption properties, drug solubility, stability as a formulation, safety in vivo, and simple and easy production process. As a result, the present inventors found out that by mixing a specific poorly-soluble drug solubilizing composition with an antipyretic, analgesic and antiphlogistic agent, a novel antipyretic, analgesic and antiphlogistic agent composition can be obtained which is extremely excellent in terms of transdermal absorption, causes no irritation, excellent in terms of safety, and which can be produced by a simple and easy production process, and consequently completed the present invention.

Among various analgesic and antiphlogistic agents, many of the drugs are highly crystalline and hardly dissolve in water or oil at high concentrations. However, the present invention provides a poorly-soluble drug solubilizing composition which dissolves these drugs at high concentrations in a transparent manner.

That is, according to the present invention, the above problems can be achieved using the following two poorly-soluble drug solubilizing compositions.

- I. A poorly-soluble drug solubilizing composition containing a medium-chain fatty acid ester of polyhydric alcohol (first invention).
- II. A poorly-soluble drug solubilizing composition containing polar oil selected from at least one lactic acid alkyl esters, dibasic acid alkyl esters, polyhydric alcohol alkyl ethers, acylated amino acids, fatty alcohols, and fatty acids (second invention).

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Second Invention

The poorly-soluble drug solubilizing composition of the second invention contains polar oil selected from at least one lactic acid alkyl esters, dibasic acid alkyl esters, polyhydric

alcohol alkyl ethers, acylated amino acids, fatty alcohols, and fatty acids, and preferably contains the aforementioned polar oil and water.

Because the poorly-soluble drug solubilizing composition of the second invention is capable of dissolving an analgesic and antiphlogistic agent, it is possible to obtain an analgesic and antiphlogistic agent composition.

While leaving the effective dose of the aforementioned polar oil, it is possible to replace the remainder thereof with a medium-chain fatty acid ester of polyhydric alcohol at an arbitrary ratio, and even in such cases, analgesic and antiphlogistic agents can also be dissolved in a similar manner.

When the solubilizing composition of the second invention includes the aforementioned polar oil and water, an antipyretic, analgesic and antiphlogistic agent can be dissolved therein up to about the same weight as the combined weight of the aforementioned oil and water.

The weight ratio of the aforementioned polar oil and water (i.e., oil/water) is preferably from 5/95 (more preferably 40/60 and still more preferably 50/50) to 95/5 (more preferably 90/10).

With respect to the water in the solubilizing compositions of the first and second inventions, an arbitrary portion thereof can be replaced with a buffer solution, and even in such cases, analgesic and antiphlogistic agents can also be dissolved in a similar manner.

Lactic acid alkyl esters are preferably esters of lactic acid and fatty alcohols having 4 to 18 carbon atoms.

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An antipyretic, analgesic and antiphlogistic agent composition which is formed by dissolving an antipyretic, analgesic and antiphlogistic agent in the solubilizing composition of the first or second invention generally appears as a transparent solution in many cases, but may also become a gel.

As an antipyretic, analgesic and antiphlogistic agent to be dissolved in the solubilizing composition of the first or second invention, for example, mefenamic acid, dichlofenac

sodium, flufenamic acid, aspirin, sodium salicylate, choline salicylate, salicyl salicylate, sulpyrine, alclofenac, ibuprofen, naproxen, flurbiprofen, ketoprofen, fenbufen, tinoridine hydrochloride, benzydamine hydrochloride, tiaramide hydrochloride, perisoxal citrate, diphenyldimethylaminoethane hydrochloride, indomethacin, ergotamine tartrate, tramadol hydrochloride, trimethine sodium, dimetotiazine mesilate, metiazinic acid, protizinic acid, clidanac, sulindac, niflumic acid, pranoprofen, aspirin DL-lysine, clonixin, fentiazac, bendazac, fenoprofen calcium, piroxicam, fentiazac, glycyrrhetinic acid, or the like is available.

If needed, in an antipyretic, analgesic and antiphlogistic agent composition, one or more materials among silicone oil, lower alcohols, water soluble polymers, inorganic powders, organic powders, surface active agents, absorbefacients, chelating agents, antioxidants, and solvents can be further added.

The addition of silicone oil results in the improvements of the problems of discomfort during use and also the development of water repellency.

The addition of lower alcohols can provide the composition with a refreshing feeling.

The addition of water soluble polymers can make the composition transparent and in an ointment-like state.

The addition of inorganic or organic powders can make the composition translucent or opaque and in an ointment-like state.

The addition of surface active agents can further improve the composition stability or enhance the absorption properties.

The addition of absorbefacients can promote the drug absorption into the body of a drug recipient even further.

The addition of chelating agents can improve the drug stability.

The addition of antioxidants can improve the stability of drugs against oxidation.

In terms of the formulation type, the antipyretic, analgesic and antiphlogistic agent composition can be made into an oral preparation, an external preparation, a suppository,

an ophthalmic solution, a liquid formulation, an ointment, a gelling agent, or a patch if needed.

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In the present invention, the above-mentioned drug only needs to be dissolved in the solubilizing composition of the first or second invention. There are no particular limitations on the method for formulating compositions. More specifically, even when the fatty acid ester of polyhydric alcohol and water or the aforementioned specific polar oil and water are not compatible with each other, the solubilizing composition of the present invention is formulated in which three components are homogenously dissolved by mixing the drug therewith. The drug is dissolved to an extent which is higher than the drug solubility to each of the fatty acid ester of polyhydric alcohol, the aforementioned specific polar oil and water, which makes the solubilizing composition novel and useful.

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The specific examples of the specific polar oil include lactic acid alkyl esters, such as octyl lactate and cetyl lactate etc.

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With respect to the water in the solubilizing compositions of the first and second inventions, purified water is more than adequate. However, for the sake of adjusting pH or the like, a buffer solution may be used if required.

In terms of the amount of the drug, the medium-chain fatty acid ester of polyhydric alcohol or the aforementioned specific polar oil and water within the antipyretic, analgesic and antiphlogistic agent composition (when containing water), the following proportions are adequate. In other words, 0.01 to 10% by weight of the drug, 0.1 to 98% by weight of the medium-chain fatty acid ester of polyhydric alcohol or the aforementioned specific polar oil, and 0.1 to 98% by weight of water are adequate, respectively; 0.1 to 10% by weight of the drug, 5 to 70% by weight of the medium-chain fatty acid ester of polyhydric alcohol or the aforementioned specific polar oil, and 10 to 80% by weight of water are preferable, respectively; and 0.1 to 10% by weight of the drug, 40 to 50% by weight of the medium-chain fatty acid ester of polyhydric alcohol or

the aforementioned specific polar oil, and 40 to 60% by weight of water are more preferable, respectively.

Either of the medium-chain fatty acid ester of polyhydric alcohol or the aforementioned specific polar oil and water can be combined in numerous ways. However, when these two components are compatible with each other at an arbitrary ratio compared to the cases where they are incompatible, not only the transparent region within the three component system which is formed by dissolving a drug in these two components widens, but also the mixing of other components becomes much easier. Accordingly, the degree of freedom for selecting the mixing ratio or the type of other components in accordance with the properties of the drug is enhanced, and thus there is a great advantage in the preparation of formulations.

When dissolving a drug in the solubilizing composition of the present invention, there are no particular limitations on the mixing method. The drug may be dispersed in any one of the medium-chain fatty acid ester of polyhydric alcohol, the polar oil or water in advance followed by the addition of another component, or 3 components may be mixed at the same time.

No particular heating process is required when dissolving a drug in the solubilizing composition of the present invention. However, for the sake of shortening the dissolution time or the like, a process of heating from 50 to 70 °C may be conducted if needed.

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Moreover, by mixing crotamiton as a solvent which serves as a crystal precipitation inhibitor, precipitation of drugs at extremely low temperatures can be prevented.

The antipyretic, analgesic and antiphlogistic agent composition of the present invention can be formed into a suitable formulation type in accordance with the administration route or administration object. That is, the composition can be used as a liquid formulation for external preparations or ophthalmic solutions. In addition, by mixing an adequate amount of the aforementioned water soluble polymer or powder, the composition can be made into an emulsified form, an ointment form or a powder form. Moreover, by encapsulating these forms in a capsule material, a capsule can also be formed.

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Example 11

Dichlofenac sodium	10.0%
Capryl lactate	40.0
Purified water	50.0

A formulation was prepared using the above combination of materials by the same method as that described in Example 1. As a result, a stable transparent formulation was obtained in a liquid form in which dichlofenac sodium was dissolved.

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Effect of Invention

Since the solubilizing composition of the second invention includes the aforementioned specific polar oil, an antipyretic, analgesic and antiphlogistic agent can be dissolved satisfactorily.

An antipyretic, analgesic and antiphlogistic agent composition which is formed by dissolving an antipyretic, analgesic and antiphlogistic agent in the solubilizing composition of the first or second invention is extremely excellent in terms of transdermal absorption properties, causes no irritation, and excellent in terms of stability as a formulation, safety in vivo, and simple and easy production process.

When the water in the antipyretic, analgesic and antiphlogistic agent composition of the present invention serves as a buffer solution, pH of the composition can be adjusted.

In the solubilizing composition of the present invention, when either of the medium-chain fatty acid ester of polyhydric alcohol or the aforementioned specific polar oil and water are compatible with each other, as compared to the cases where they are incompatible, not only the transparent region within the three component system which is obtained by dissolving an antipyretic, analgesic and antiphlogistic agent in these components widens, but also the mixing of other components becomes much easier. Accordingly, the degree of freedom for selecting the mixing ratio or the type of other components in accordance with the properties of the drug is enhanced, and thus there is a great advantage in the preparation of formulations.

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When the solvent is crotonol, precipitation of drugs at extremely low temperatures can be prevented.

Claims

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6. A poorly-soluble drug solubilizing composition characterized in that the composition contains polar oil selected from at least one lactic acid alkyl ester, dibasic acid alkyl ester, polyhydric alcohol alkyl ether, acylated amino acid, fatty alcohol, or fatty acid.
7. The poorly-soluble drug solubilizing composition according to Claim 6, in which the composition contains the polar oil and water.
8. The poorly-soluble drug solubilizing composition according to Claims 6 or 7, in which a part of the oil is replaced with a medium-chain fatty acid ester of polyhydric alcohol.
9. The poorly-soluble drug solubilizing composition according to Claims 2 or 7, in which the water is replaced with a buffer solution.
10. The poorly-soluble drug solubilizing composition according to Claims 6 or 7, in which the lactic acid alkyl ester is an ester of lactic acid and fatty alcohol having 4 to 18 carbon atoms.

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